Quality by Design in process development and scale-up for lyophilized parenteral products

Quality by Design in Process Development and Scale-up for Lyophilized Parenteral Products

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Purpose: In the last decade FDA invited pharmaceutical industry to modernize their manufacturing, applying the most recent Process Analytical Technologies and the Quality by Design paradigm. The final goal is the promotion of more efficient and cost-effective processes, building drug product quality within the process rather than testing it off-line at the end of the process (1). This article shows how this goal can be achieved in the case of freeze-drying of parenteral products. In particular, the problem of design and scale-up is shown for a real case in industry, i.e., the freeze-drying of an antiviral drug. Examples are given of cycles designed varying either freezing conditions or scale of equipment.

Methods: A non-steady state mathematical model, parameterized with experimentally determined heat and mass transfer coefficients, was used to manipulate the critical process parameters within predefined limits of the so-called "design space" (2). The overall heat transfer coefficient was determined by gravimetric procedure, while the resistance to vapor flow through the product temperature response method. Calculations could also recognize equipment and product constraints, and take into account model parameter uncertainty. Mathematical modeling was finally used to expedite scale-up operations, so as to transfer lyophilization cycles from small-scale equipment to manufacturing scale (3).

Results: Figure 1 shows an example of design space for primary drying of an antiviral drug in the case of two freezing protocols: (a) shelf-ramped freezing and (b) shelf-ramped freezing + annealing. Annealing promoted the formation of larger ice crystals, smaller resistance to mass transfer, and hence resulted in enlargement of design space. It follows that the cycle with annealing can be carried out at higher shelf temperature and pressure, reducing the drying time while still satisfying drug product quality. The cycle with annealing was then scaled-up in the industrial equipment, replicating the same thermal history observed in the small-scale dryer (data not shown). The scaled-up cycle needed a higher shelf temperature so as to replicate, in the industrial unit, temperature profile and drying time observed in the lab-scale equipment. The impact of inter-vial variability on design space, and thus on the optimized cycle, could also addressed.

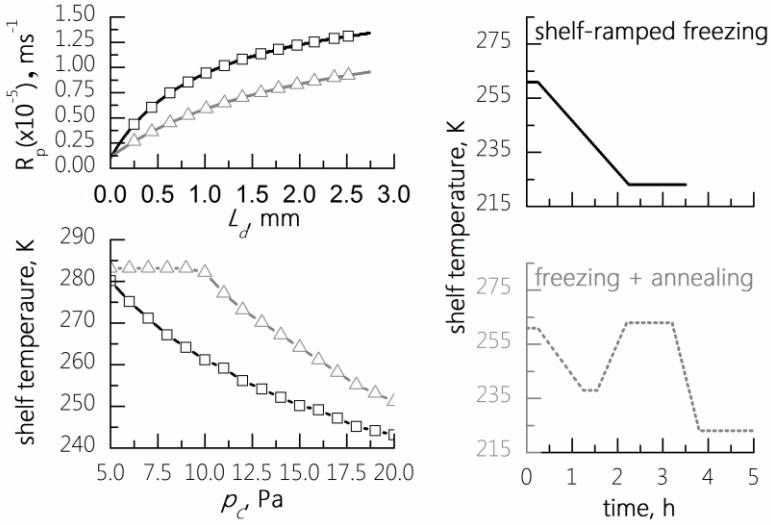

Figure 1. (Left-graph) Resistance to mass transfer (top) and design space (bottom) in the case of shelf-ramped freezing with (right, top graph) and without annealing (right, bottom graph; grey curves).

Conclusions: The use of mathematical modeling is demonstrated to be very effective not only for cycle development, but also for solving problem of process transfer. Furthermore, the use of mathematical modeling can reduce the experimental effort required for system qualification.

References:

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3. Pisano R., Fissore D., Barresi A.A., Brayard P., Chouvenc P., Woinet B. Pharmaceutical Development and Technology. 2013 (18) 280-295.